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reference in their entirety for all purposes. This application is also related to U.S. Patent Application No. 09/243,104, filed February 2, 1999 (Attorney Docket No. 016303-006220), which is incorporated herein by reference in its entirety for all purposes.--

REMARKS

Claims 1-34 are pending in the above-identified patent application; claims 1-28 are currently under examination. In the Office Action dated April 10, 2000, claims 3-7, 11 and 16 were rejected under 35 U.S.C. § 112, second paragraph, and claims 1-28 were rejected under 35 U.S.C. § 112, first paragraph. Each of these rejections is addressed in turn below.

RESTRICTION REQUIREMENT

Applicants hereby affirm the election of Group I, claims 1-28, drawn to a method of treating a neoplasm, made by Applicants' representative on January 18, 2000 and referenced on page 2 of the Office Action mailed April 10, 2000. This election is made with traverse as the two groups set out by the Examiner stem from a common concept and theory and are thus related. As such, prosecution of the claims of Groups I and II together would not place a substantially greater burden on the Examiner.

PRIORITY CLAIM

In the Office Action, the Examiner has indicated that it is unclear whether Applicants intend to claim priority to U.S. Provisional Patent Application Nos. 60/112,384 and 60/073,598. The Examiner has further indicated that if Applicants do intend to claim priority to such applications, reference should be made to them in the first sentence of the above-identified patent application.

In accordance with the Examiner's suggestion, Applicants have amended the first sentence of the above-identified patent application so that it makes reference to and claims priority to U.S. Provisional Patent Application Nos. 60/112,384 and 60/073,598. In view of this amendment, the Examiner's concern is overcome.

OBJECTION TO THE SPECIFICATION

In the Office Action, the Examiner has noted that the first paragraph of the specification makes reference to a related, co-pending U.S. patent application, but that the application number has not been provided.

In order to expedite prosecution, Applications have amended the first paragraph of the specification to incorporate the appropriate application number, *i.e.*, 09/243,104, for the related, co-pending U.S. patent application that bears Attorney Docket No. 016303-006220.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 3-7, 11 and 16 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Each of the Examiner's concerns and, in turn, Applicants responses to those concerns will be addressed below.

a. The Examiner has rejected claim 3 as indefinite, stating that it is unclear how "an expressible gene necessarily encodes a 'therapeutic' polynucleotide" (*see*, page 4 of the Office Action.)

Applicants respectfully submit that the meaning of this phrase is clear and definite to those of skill in the art from a reading of the specification either alone or coupled with the general knowledge in the art. As set forth in the specification, the phrase "gene product" refers to:

> [A] product of a gene such as an RNA transcript. The RNA transcript can be therapeutic of its own accord as in the case of antisense or ribozyme transcriptional plasmids, or the RNA transcript can be translated into a polypeptide that is also a gene product.

See, page 7, lines 26-29 of the specification. As such, Applicants respectfully submit that the language of claim 3 is both clear and definite to those of skill in the art.

b. The Examiner has rejected claim 4 as indefinite, stating that the meaning of the term "exogenous" is unclear.

Applicants respectfully submit that the term "exogenous" is a term of art that is routinely used by those of skill in the art and, thus, its meaning does not have to be set forth in the claims and/or in the specification. Clearly, those of skill in the art know that the phrase

"said gene is exogenous" refers to a gene that is foreign to the mammal or cell. As such, Applicants respectfully submit that the language of claim 4 is both clear and definite to those of skill in the art.

c. The Examiner has rejected claim 5 as indefinite, stating that the phrase "suicide enzyme" is unclear.

Applicants respectfully submit that the meaning of this phrase is clear and definite to those of skill in the art from a reading of the specification either alone or coupled with the general knowledge in the art. As explained in the specification, the "suicide enzyme" is part of gene-delivered enzyme prodrug therapy ("GDEPT") or, alternatively, the suicide gene/prodrug system. In one embodiment of GDEPT, a gene is delivered to a cell, the gene encoding an enzyme that promotes the metabolism or processing of a first compound to which the cell is less sensitive (*i.e.*, the prodrug) into a second compound to which the cell is more sensitive. This enzyme is referred to by those of skill in the art as the "suicide enzyme." The specification and claims set forth numerous examples of suicide enzymes that can be used in carrying out the methods of the present invention (*see, e.g.*, page 4, lines 21-30, of the specification). As such, Applicants respectfully submit that the language of claim 5 is both clear and definite to those of skill in the art.

d. The Examiner has rejected claim 6 as indefinite, stating that the term "analog" is unclear.

Applicants respectfully submit that the term "analog" is a term of art, and its use in claim 6 is clear and definite to those of skill in the art. Clearly, those of skill in the art know that the term "analog" refers to compounds having a structure and properties similar to those compounds recited in claim 6. Those of skill in the art can readily identify such compounds based on their structural similarity and, in addition, they can readily screen such compounds to ensure they have desirable properties. As such, the language of claim 6 is both clear and definite.

e. The Examiner has rejected claim 7 as indefinite, stating that the term "homologous" is unclear.

As with the term "exogenous," Applicants respectfully submit that the term "homologous" is a term of art that is routinely used by those of skill in the art and, thus, its meaning does not have to be set forth in the claims and/or in the specification. Clearly, those of skill in the art know that the phrase "said gene is homologous" refers to a gene that is not foreign to the mammal or cell, *i.e.*, it is endogenous. As such, Applicants respectfully submit that the language of claim 7 is both clear and definite to those of skill in the art.

f. The Examiner has rejected claim 11 as indefinite, stating that the phrase "protonatable lipid" is unclear.

Applicants respectfully submit that the phrase "protonatable lipid" is another term of art and those of skill in the art understand its meaning. Clearly, a protonatable lipid is one that can be protonated. Moreover, the specification and claims specifically set forth that the protonatable lipid has a pKa in the range of about 4 to about 11. In addition, the specification and claims recite numerous examples of protonatable lipids (*see, e.g.*, claim 12). As such, Applicants respectfully submit that the language of claim 11 is both clear and definite to those of skill in the art.

g. The Examiner has rejected claim 16 as indefinite, stating that the phrase "substantially devoid" is unclear.

Applicants respectfully submit that the meaning of the phase "substantially devoid" is clear to those of skill in the art. The term "substantially" is a term of degree. When a term of degree is present in a claim, a determination must first be made as to whether the specification provides a standard for measuring that degree (*see*, MPEP 2173.05(b)). According to the Federal Circuit, the standard is "whether one of skill in the art would understand what is claimed when the claim is read in light of the specification" (*see, Seattle Box Company, Inc. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed. Cir. 1984)). In this Federal Circuit case, a claim to substantially increase the efficiency of a compound as a copper extractant was found to satisfy the definiteness requirement of 35 U.S.C. § 112, second paragraph, because the specification allowed one of skill in the art to practice the invention.

In the present case, the specification provides more than sufficient teachings to allow those of skill in the art to make and use the claimed invention. Clearly, the specification teaches how to make the lipid-nucleic acid particles used in the claimed methods (*see, e.g.*,

Example 1, wherein five different formulations are disclosed). In addition, based on the teachings of the specification, those of skill in the art can clearly make lipid-nucleic acid particles that are substantially free of detergents and organic solvents. As such, Applicants respectfully submit that the language of claim 16 is both clear and definite to those of skill in the art.

In view of the foregoing remarks, each of the Examiner's concerns is overcome. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, second paragraph.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-28 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. In the Office Action, the Examiner alleges that the present claims are not enabled over the full scope of the claims. In this regard, the Examiner raises the following concerns: (1) that "the art of gene delivery and expression is in its infancy and highly unpredictable" (*see*, pages 5-8 of the Office Action); and (2) that "the specification fails to teach the successful delivery and expression of expressible genes in any immunologically competent organisms such that treatment effects are provided" (*see*, pages 8-10 of the Office Action). Applicants respectfully traverse this rejection.

A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without undue experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of

> guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06, citing *In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988).

In the present case, Applicants submit that none of the potential issues raised by the Examiner in the Office Action would have required one of skill to practice an undue amount of experimentation in order to practice the invention.

Applicants note, first of all, that the present specification provides extensive guidance, including working examples, for practicing the claimed invention. For example, page 10, line 14 to page 14, line 24 provides teachings regarding therapeutic nucleic acids, and page 14, line 25 to page 18, line 31 provides teachings regarding the preparation and properties of the lipid/therapeutic nucleic acid particles. In addition, page 19, line 28, to page 20, line 16, provides teachings regarding the disease indications suitable for treatment using the lipid-nucleic acid particles of the present invention, and page 20, line 17, to page 21, line 21, provides teachings regarding combination therapies that can be used with the lipid-nucleic acid particles of the present invention. Page 19, line 1, to page 19, line 27, provides teachings regarding administration-ready pharmaceutical preparations, and page 21, line 20, to page 22, line 27, provides teachings regarding the administration of the lipid-nucleic acid particles.

Further, the specification provides numerous examples describing, *e.g.*, the preparation of lipid-plasmid particles (Examples 1 and 4), the delivery of lipid-formulated ganciclovir to mice having tumor cells transfected with HSV-TK (Examples 2, 3, 4A, and 11), the delivery and detection of nucleic acids to tumor cells *in vivo* (Examples 6, 11, 13, 14 and 15), the delivery of lipid-formulated TK-encoding plasmids and ganciclovir to mice harboring tumor cells (Example 7), and the preparation, pharmacokinetics, and biodistribution of lipid-formulated ganciclovir (Examples 8, 9 and 10). Taken together, such examples unequivocally establish that the lipid-nucleic acid particles of the present invention are capable of transforming cells and effecting phenotypic changes such as reduction in tumor proliferation and size.

It is noted that many of these examples are working examples performed in model animals, providing clear evidence of the enablement of the claimed methods as required

by the case law. For example, in *In re Jolles*, 206 USPQ 885 (CCPA 1980), the CCPA stated that:

> This court recognizes 'that a demonstration that a compound has desirable or beneficial properties in the prevention, alleviation, or cure of some disease or manifestation of a disease in experimental animals does not necessarily mean that the compound will have the same properties when used with humans.' ***However, this is by no means support for the board's position that such evidence is not relevant to human utility.***
>
> To the contrary, this court has accepted tests on experimental animals as ***sufficient to establish utility***.... *Id.* at 890 (citations omitted; emphasis added).

Applicants respectfully submit that the extensive guidance provided in the specification, and the presence of numerous working examples in an animal model, are thus sufficient to establish the enablement of the present claims.

Despite this guidance provided in the specification, however, the Examiner alleges that the present claims are not enabled over the full scope of the claims. In this regard, the Examiner raises the following two concerns: (1) that "the art of gene delivery and expression is in its infancy and highly unpredictable" (*see*, pages 5-8 of the Office Action); and (2) that "the specification fails to teach the successful delivery and expression of expressible genes in any immunologically competent organisms such that treatment effects are provided" (*see*, pages 8-10 of the Office Action).

In support of the first concern, the Examine cites a number of references that allegedly demonstrate that gene therapy are unpredictable and surrounded by significant hurdles. However, a perusal of the cited references reveals that contrary to the Examiner's allegation, such references ***support*** the proposition that gene therapy works. For instance, Crystal *et al.* state at page 405 that:

> Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible. Although gene transfer has not been demonstrated in all recipients, ***most studies have shown that genes can be transferred to humans whether the strategy is ex vivo or in vivo, and that all vector types function as intended.*** Taken together, the evidence is ***overwhelming***, with successful gene transfer having been demonstrated in 28 ex vivo and ***10 in vivo studies***" (emphasis added).

Similarly, Varma *et al.* state at page 242 that:

> So how far have we come since clinical trials began? The promises are still great, and the problems have been identified (***and they are surmountable***). But what of the prospects? ***Our view is that, in the not too distant future, gene therapy will become as routine a practice as heart transplants are today*** (emphasis added).

In addition, Friedmann states at page 101 that:

> Gene transfer by liposomes (or 'lipoplexes,' as current versions are increasingly called) is much less efficient than virus-mediated transfer but has advanced enough for these vectors to enter clinical trials for such diseases as cancer and cystic fibrosis. ***Meanwhile alterations in the chemical compositions of liposomes are addressing the efficiency problem and are beginning to produce vectors that mimic viruses in their targetability and prowess at gene transfer*** (see 'Nonviral Strategies for Gene Therapy,' by Philip L. Felgner, on page 102) (emphasis added).

Moreover, with respect to the treatment of cardiovascular diseases using liposome-mediated gene delivery, Schofield *et al.* state at page 64 that:

> The future of cationic liposome-mediated gene delivery to the cardiovascular system looks promising in the light of these recent developments.

Thus, the foregoing statements coupled with Applicants' examples showing the ability of the lipid-nucleic acid particles of the present invention to deliver genes and drugs to distal tumor cells and to reduce or prevent tumor grow clearly demonstrate that gene therapy works. Again, Applicants examples unequivocally establish that the lipid-nucleic acid particles of the present invention are capable of transforming cells and effecting phenotypic changes such as reduction in tumor proliferation and size.

With respect to the Examiner's second concern, it has been alleged that "the specification fails to teach the successful delivery and expression of expressible genes in any immunologically competent organisms such that treatment effects are provided" (*see*, pages 8-10 of the Office Action). Applicants ***disagree***.

More particularly, it is respectfully pointed out that the mice used in Applicants' experiments, *e.g.*, C57 mice, are ***not*** immunocompromised, *i.e.*, they are immunologically

competent organisms. As such, the Examiner's statement at the bottom of page 8 of the Office Action is ***correct*** except for the phrase "in immunocompromised mice." Clearly, Applicants examples unequivocally establish that the lipid-nucleic acid particles of the present invention are capable of transforming cells and effecting phenotypic changes ***in immunologically competent organisms***. As such, the Examiner's second concern is entirely misplaced.

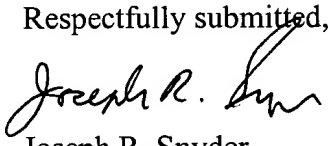
In view of all of the above, Applicants assert that the presently pending claims are fully enabled by the specification under 35 U.S.C. 112, first paragraph. Accordingly, Applicants respectfully request that the rejection under 112, first paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
EGW:lls
SF 1144926 v1